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BLOOD pH AND pCO_2 HOMEOSTASIS IN CHRONIC RESPIRATORY ACIDOSIS RELATED TO THE USE OF AMINE AND OTHER BUFFERS

by

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SUMMARY PAGE

THE PROBLEM

To present data and discuss the problem of control of carbon dioxide in the submarine atmosphere, especially concerning the use of amine buffers for the control of this problem.

FINDINGS

In World War II, when no adequate CO_2 removal equipment existed, concentrations of 3-5% had to be tolerated over extended periods. Attempts to remedy the situation by using alkaline buffers were made and found helpful only in alleviating symptoms related to the pH changes of the uncompensated phase of respiratory acidosis. Results of prolonged exposure to 1.5% CO_2 (for periods of 42 days as in Operation Hideout) demonstrated that the elevated pCO_2 persisting during the compensated phase of respiratory acidosis has significant effects on a number of physiological functions, independent of pH, and this condition is not amenable to treatment by amine buffers.

APPLICATION

The use of nuclear-powered submarines capable of greatly extended periods of submergence requires a solution to the carbon dioxide problem. The results of this study will contribute to effective control of this situation.

ADMINISTRATIVE INFORMATION

This investigation was undertaken as a part of Bureau of Medicine and Surgery Research Task MR005.14-3002-1, Physiological Mechanisms of CO_2 Toxicity. The present report is No. 7 on this Subtask. It was published in the Annals of the New York Academy of Medicine, Vol. 92, Art. 2, 401-413, June 1961.

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BLOOD *p*H AND pCO_2 HOMEOSTASIS IN CHRONIC RESPIRATORY ACIDOSIS RELATED TO THE USE OF AMINE AND OTHER BUFFERS

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This report deals with the use of amine buffers in the CO_2 scrubber of submarines and the problems of chronic CO_2 toxicity as they relate to treatment with buffers. I propose to discuss the CO_2 control of the submarine atmosphere very briefly, since I can only provide some general information on this subject based on the work of engineers at the Naval Research Laboratory, Washington, D.C. I shall present data on the homeostasis of *p*H and pCO_2 obtained during the prolonged exposure of 23 subjects to 1.5 per cent CO_2 that indicate the effects of elevated pCO_2 independent of *p*H changes. Only the latter are subject to treatment with amine buffers. Moreover I shall mention earlier attempts to use alkalinizing agents, such as potassium salt, to increase the tolerance to hypercapnia.

Atmospheric Control with CO_2 Scrubbers Using Amine Buffers

Chronic CO_2 toxicity is known to have been a cardinal problem of submarine medicine for many years, simply because no technical advances were made to develop efficient self-regulating CO_2 removal equipment. With the advent of nuclear-powered submarines capable of greatly extended submergence times, it was necessary to find a solution. The introduction of a CO_2 scrubber using monoethanolamine represented the first satisfactory accomplishment to remove CO_2 with self-regenerating absorbent. Monoethanolamine (MEA) absorbs CO_2 at room temperature and releases it at higher temperature. A simplified diagram of the amine-type CO_2 removal equipment is presented in FIGURE 1. It consists of an absorber column, a CO_2 stripper, an amine pump, and a heat exchanger. The submarine air is pumped through a cool MEA solution in the absorber column and CO_2 is chemically absorbed. The MEA solution is recycled through the absorber column. Part of the MEA solution is piped to the CO_2 stripper, where it is heated under pressure to release the CO_2. The latter is further compressed and discharged overboard. The hot MEA is cooled and used again in the absorber. The CO_2 scrubbers presently in operation have a capacity to remove 10 lb. of CO_2/hour while operating at 170 c.f.m.

FIGURE 2 shows a comparison of a conventional lithium hydroxide (LiOH) scrubber used on battery-powered submarines with an MEA system in regard to weight, volume, and power requirements. It is obvious that the LiOH system has an advantage for short periods up to 10 days. For the longer periods, the MEA scrubber is of course the better choice.

According to Goodridge,[2] it is believed that mono- and diethanolamines react with CO_2 by donating an electron of a hydrogen molecule from the amine linkage and formation of carbonates. Since the molecular weight of monoethanolamine is much smaller than that of diethanolamine and triethanolamine

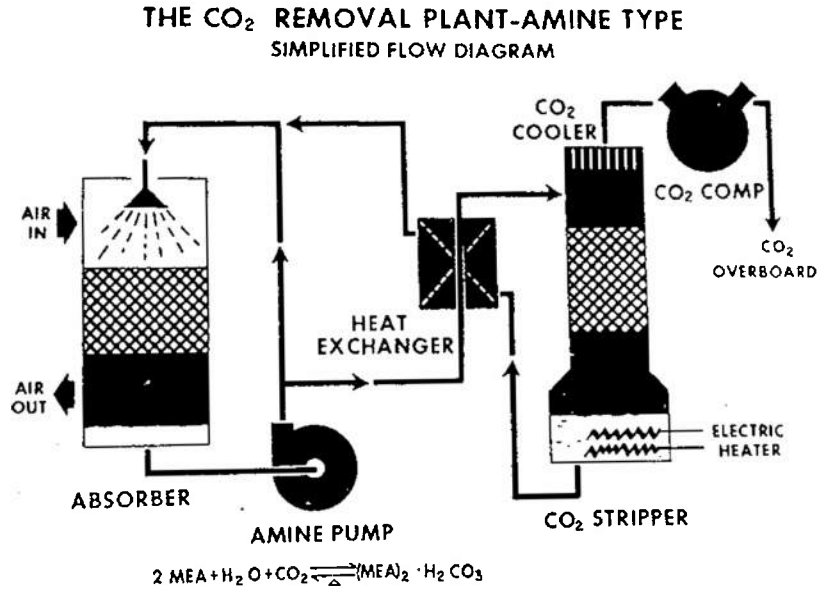

FIGURE 1. Diagram of an amine-type CO_2 scrubber. (Reproduced by permission of The Macmillan Co., New York, N.Y.[1])

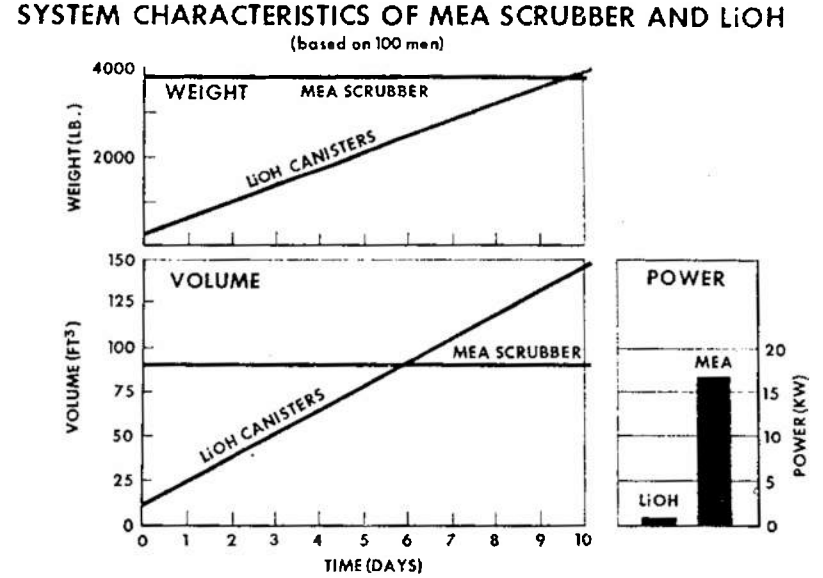

FIGURE 2. Weight, volume, and power requirements of MEA and LiOH CO_2 scrubbers calculated for 100 men. (Reproduced by permission of The Macmillan Co., New York, N.Y.[1])

and only 1 mol. of amine is utilized per molecule of CO_2 reacted, the relative absorption capacity of CO_2 per pound is much greater for MEA (1.0:0.58:0.41). MEA leaves something to be desired as a regenerative carbon dioxide absorbent. It has a lack of resistance to oxidation that in time leads to a degradation of the MEA solution requiring replacement. Furthermore, MEA has a certain toxicity. The current maximal allowable concentration (MAC) established by the Bureau of Medicine and Surgery for the United States Navy is 1 ppm.*

Blood pH and pCO_2 Homeostasis During Prolonged Exposure to Increased CO_2 Levels

In World War II, when no adequate CO_2 removal equipment existed in submarines to allow prolonged submergences, CO_2 concentrations of 3 to 5 per cent had to be tolerated over extended periods. It was during this time that interest was developed in using alkali buffers to make men CO_2 resistant and, eventually, to raise the tolerance to CO_2 in submarine crews. These early attempts to treat respiratory acidosis with Na and K buffers will be discussed later. I shall concentrate first on the results of studies that produced evidence that the effects of increased pCO_2 independent of pH changes are significant. In emphasizing the aspects of pCO_2 homeostasis, which is not influenced by alkali or Tris buffer medication, it is hoped that a useful contribution may be made to define the limitations and indications for the use of Tris buffer in respiratory acidosis.

In a large experiment 23 subjects were confined in a submarine and exposed to 1.5 per cent CO_2 in 21 per cent O_2 over a period of 42 days, with a 9-day control period prior to and following exposure. The results showed no significant changes in performance[3] or in basic physiological parameters, such as blood pressure, pulse rate, weight, and body temperature (FIGURE 3). However, studies of respiration,[4] acid-base balance, and electrolyte exchange[5] brought some unexpected findings. A slight uncompensated respiratory acidosis existed for a period of 23 days after which the pH returned to normal. During a 9-day recovery period following a 42-day exposure to 1.5 per cent CO_2 the alveolar pCO_2, blood pCO_2 remained elevated at the level reached during exposure. The existence of a phase of uncompensated respiratory acidosis for 23 days followed by a phase of compensated respiratory acidosis from the 24th to the 42nd day is indicated in FIGURE 4 in the changes of pH, of blood and urine, and CO_2 excretion in the urine. Moreover a significant depression of the respiratory response to 5 per cent CO_2, previously described as part of a respiratory adaptation to CO_2,[6] was found after 35 days of exposure to 1.5 per cent CO_2 (FIGURE 3). The central importance of the respiratory pattern in adaptation to CO_2[7] was demonstrated in a progressive increase in tidal volume throughout the 42 days of exposure and a decline of respiratory rate during the second phase subsequent to a transient increase during the first (uncompensated) phase of respiratory acidosis. This pattern of respiration is so strongly established at the end of a 42-day exposure to 1.5 per cent CO_2 that transition to air is not able to bring it back to normal. Contrary

* E. A. Ramskill, Naval Research Laboratory, Washington, D.C. Personal communication.

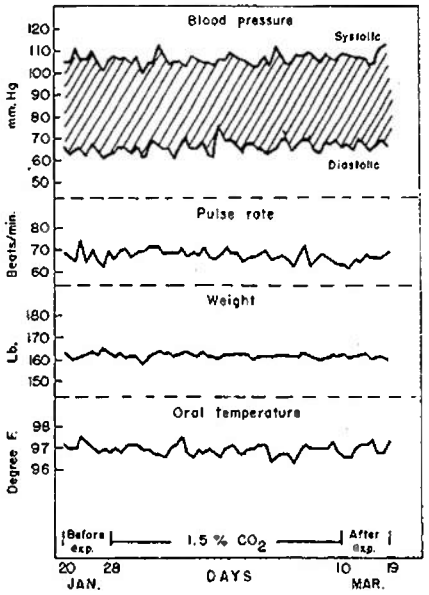

FIGURE 3. Effect of prolonged exposure to 1.5 per cent CO_2 over a period of 42 days on systolic and diastolic blood pressure, pulse rate, body weight, and oral temperature (mean values of 23 subjects). (Reproduced by permission of *Aerospace Medicine.*)

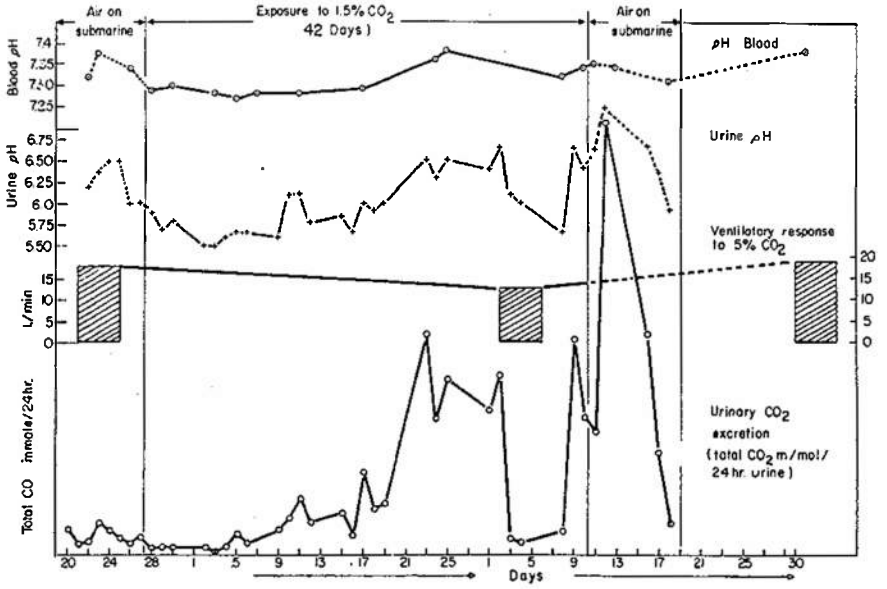

FIGURE 4. Effect of prolonged exposure to 1.5 per cent CO_2 over a period of 42 days on *p*H of blood and urine, CO_2 excretion in the urine, and ventilatory response to 5 per cent CO_2 (21 subjects). (Reproduced by permission of *Aerospace Medicine.*)

to expectation, a further drop in respiratory rate occurs, and the alveolar pCO$_2$ level is maintained at an elevated point for 9 days after return to air breathing (FIGURE 6). We therefore have two periods: (1) the compensated phase of respiratory acidosis from the 24th day to the 42nd day of exposure; and (2) the 9-day recovery period on air following exposure to CO_2, in which the pH is practically normal and the pCO$_2$ is elevated, while the blood pH changes are limited to the first 23 days of exposure.

It therefore appears possible to delineate those functions that are particularly influenced by the pH changes of the blood from those that seem to be effected

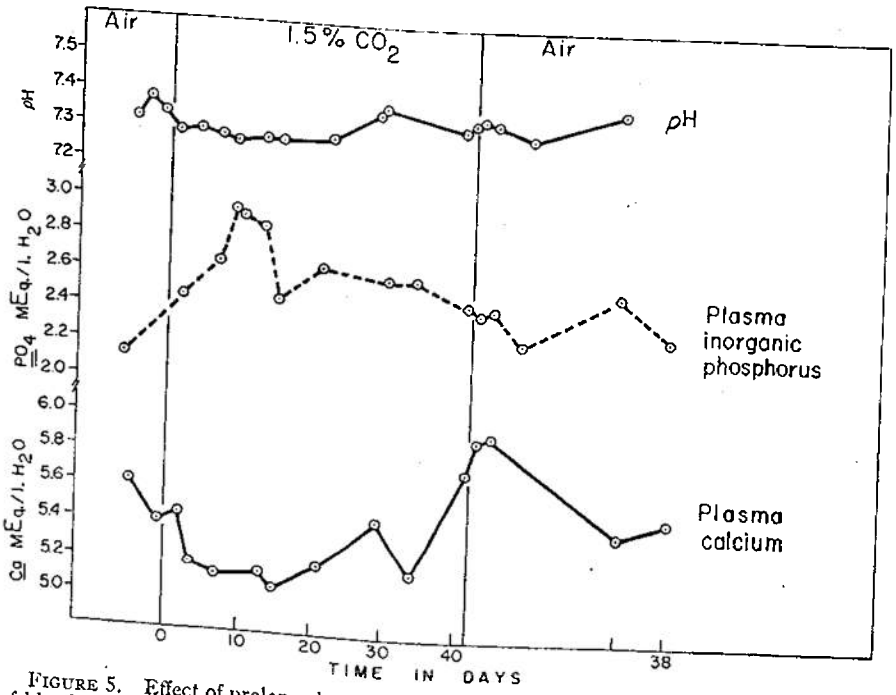

FIGURE 5. Effect of prolonged exposure to 1.5 per cent CO_2 over a period of 42 days on pH of blood plasma, inorganic phosphorus, and plasma calcium.

predominately from pCO$_2$ changes. An example of pH-dependent variables is seen in the changes of plasma calcium that mirror the alterations in blood pH (FIGURE 5). The plasma inorganic phosphorus shows the opposite trend.

FIGURE 6 shows some other physiological parameters that appear to be independent of pH changes or that, still better, are not influenced by the return of blood pH to normal. This is the pattern of respiration already mentioned above. The elevated pCO$_2$ seems to be the dominant factor in the development of a large tidal volume and a small respiratory rate, a pattern that in turn maintains an elevated pCO$_2$ as seen in the recovery period.

The cardiovascular capacity was tested with the Harvard step-up test, consisting of stepping 20 times within 30 sec. on an 18-inch high stool. Pulse

rate was counted immediately after the test, and 2 min. later. Cardiovascular score was computed as follows:

15 sec. to 20 sec. pulse rate plus
(1 min. 45 sec. to 2 min. 15 sec. pulse rate)

It can be noted that the cardiovascular score increases throughout the exposure to CO_2, indicating a reduction in cardiovascular capacity. The cardiovascular score continues to rise after the compensation of respiratory acidosis is reached.

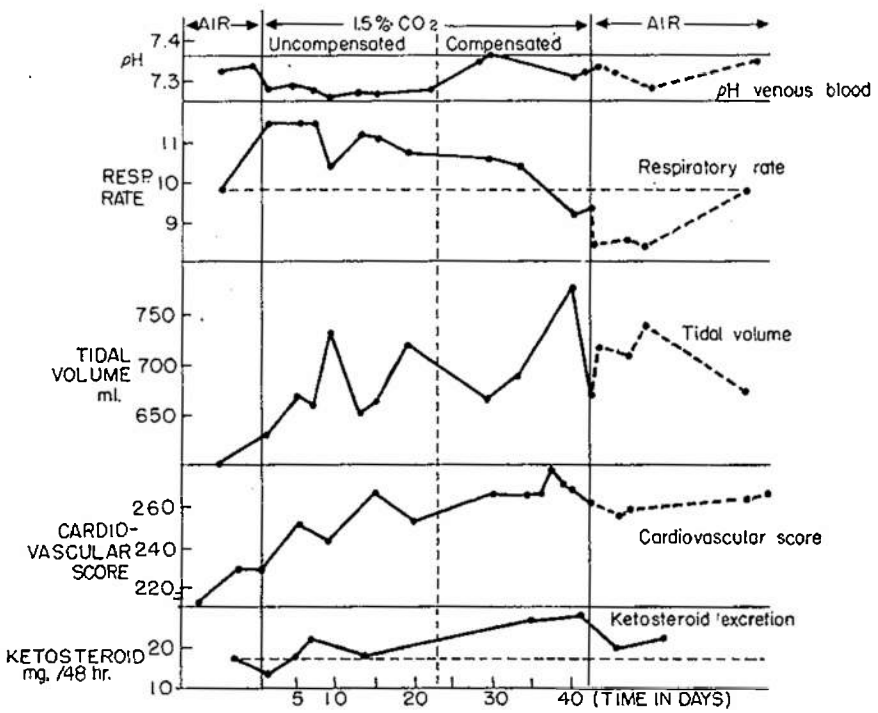

FIGURE 6. Effect of prolonged exposure to 1.5 per cent CO_2 over a period of 42 days on respiratory rate, tidal volume, cardiovascular score, and ketosteroid excretion (21 subjects).

and remains high in the recovery phase associated with the elevated pCO_2 level.[8]

As a measure of the stress of CO_2 exposure, the ketosteroid excretion[9] was measured and found higher in the compensated phase of respiratory acidosis. The eosinophils also began to fall during this second phase, reaching the lowest value during the 9-day recovery period.[9] It could be argued that the factor of confinement might have caused these effects, rather than the elevated pCO_2 levels. However, the results of animal experiments carried out simultaneously under the same conditions of exposure to 1.5 per cent CO_2 on rats and guinea pigs showed similar findings, a significant increase in adrenal-cortical activity during the same two periods in which the pH was not different from control levels and the pCO_2 elevated.[10]

Effects of Alkalinizing Agents in Chronic Respiratory Acidosis Induced by Prolonged Exposure to 2 to 3.5 per cent CO_2

These experiments were carried out by R. Pointner.[11] Some of these data on individual subjects were summarized and statistically evaluated, and are reported here. The subjects were exposed for 4 days to 2 to 3.5 per cent carbon dioxide. There was a control period on air lasting for 2 to 3 days prior to exposure, and a 3-day recovery period on air following exposure. Measurements were made during these 3 periods of urinary *p*H and of excretion of CO_2 and ammonia; determinations were also made of intake and excretion of sodium, potassium, chloride, phosphorus, calcium, and water.

TABLE 1 shows the effects of these alkalinizing agents on urinary *p*H, CO_2, and ammonia excretion prior, during, and after chronic respiratory acidosis

TABLE 1*

EFFECT OF ALKALINIZING AGENTS† ON URINARY *p*H, CO_2, AND AMMONIA EXCRETION PRIOR, DURING, AND AFTER CHRONIC RESPIRATORY ACIDOSIS (FOUR SUBJECTS)

		*p*H			CO_2 (total) gm.			Ammonia		
		---	Na salt	K salt	---	Na salt	K salt	---	Na salt	K salt
Control period on air 2 to 3 days	Mean	6.36	6.25	6.30	5.95	6.4	13.5	623	663	555
	SD	0.17	0.07	0.42	1.2	0.36	13.3	64	109.5	48.8
	N	4	2	2	4	2	2	4	2	2
Exposure to 2 to 3.5% CO_2 for 4 days	Mean	6.14	6.81‡	6.90	7.7	38.7§	79.0‡	741	443	461
	SD	1.14	0.09	0.00	2.03	0.64	7.3	156	15.6	14.9
	N	4	2	2	4	2	2	4	2	2
Recovery period on air following CO_2 exposure 3 days	Mean	6.35	6.51	6.58	8.6	15.5	26.3	528	685	436
	SD	0.14	0.44	0.02	4.5	5.1	4.1	99	35.8	17.7
	N	4	2	2	4	2	2	4	2	2

* Adapted from Pointner.[11]
† Na salt (Sepdelen 7) and potassium salt.
‡ Values significantly different from control values at the 5 per cent level and better.
§ Values significantly different from control values at the 1 per cent level and better.

combined with the results of an experiment in which no medication was used. TABLE 2 gives some information about the retention of electrolytes based on the difference between intake and urinary excretion. Unfortunately no measurements of electrolytes in feces were made, consequently no complete balance could be established.*

The sodium salt Sepdelen 7 normally has diuretic effects that were not present under conditions of CO_2 exposure in which a water retention was found (TABLE 1). There was an increased chloride and potassium excretion under CO_2 exposure, but no significant change in sodium excretion. Alkalinizing effects of sodium salt medication were shown in an increase of *p*H and the CO_2 excretion of the urine and a decrease of the ammonia excretion. The results

* The potassium phosphorus salt consisted of two thirds potassium carbonate and one third potassium biphosphate; the sodium salt (Sepdelen 7) consisted of 22 per cent sodium citrate, 23 per cent sodium tartrate, 26 per cent sodium sulphate, 25 per cent secondary sodium phosphate, and 4 per cent sodium carbonate.

TABLE 2*

EFFECT OF ALKALINIZING AGENTS† ON THE EXCHANGE OF H_2O, K, Na, Cl, AS INDICATED IN THE DIFFERENCE BETWEEN INTAKE (FOOD) AND URINARY EXCRETION

		H_2O			K			Na			Cl		
		---	Na salt	K salt	----	Na salt	K salt	----	Na salt	K salt	----	Na salt	K salt
Control period on air 2 to 3 days	Mean	322	270	680	3.01	3.86	1.40	0.36	0.38	0.46	−0.412	−0.21	−1.08
	SD	199	127	67	0.86	0.51	1.01	0.46	0.88	0.10	0.32	0.97	1.31
	N	4	2	2	4	2	2	4	2	2	4	2	2
Exposure to 2 to 3.5% CO_2 for 4 days	Mean	600	580	700	1.93	0.07	2.57	1.83	0.88	1.00	0.29	3.13	0.254
	SD	183	169	149	1.04	0.37	0.15	0.73	1.3	0.06	0.70	4.13	0.18
	N	4	2	2	4	2	2	4	2	2	4	2	2
Recovery period on air following CO_2 exposure 4 days	Mean	555	200	1010	2.42	1.05	1.39	2.11‡	−0.90	1.8	1.92‡	1.19	1.40
	SD	136	297	113	1.92	0.67	0.96	0.64	1.1	1.24	0.51	3.03	0.10
	N	4	2	2	4	2	2	4	2	2	4	2	2

* Adapted from Pointner.[11]

† Na salt (Sepdelen 7) and potassium salt.

‡ Values significantly different from control values at the 5 per cent level and better.

of potassium salt medication were somewhat similar to those of sodium salt treatment. The normally diuretic effect of potassium salt was not maintained during CO_2 exposure. Chloride excretion was reduced, and a slight increase in retention of potassium and sodium was noted. The alkalinizing effect was demonstrated in the increase of pH and CO_2 in the urine, as well as in the decrease of ammonia excretion.

The CO_2 dissociation curves of whole blood were taken under the same experimental conditions. Venous blood was equilibrated with 30, 40, and 50

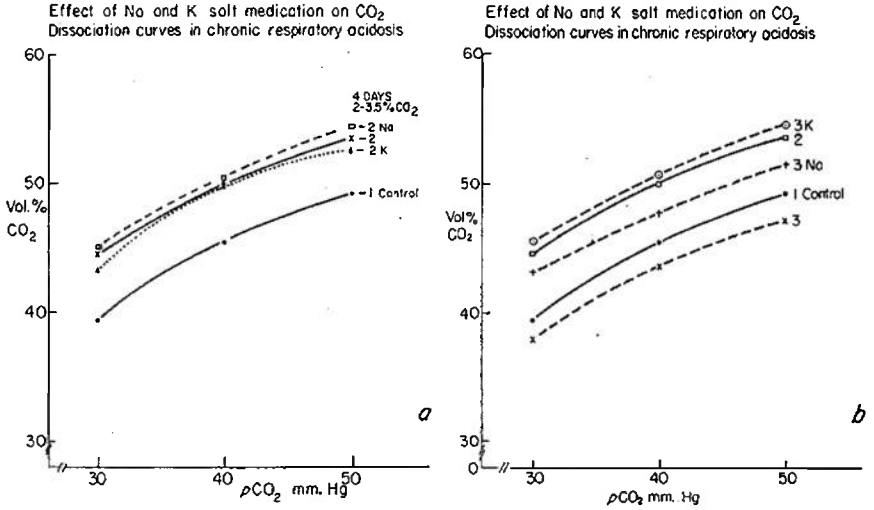

FIGURE 7(*a*). Effect of alkalinizing agents (Na salt and K salt) on CO_2 dissociation curves in chronic respiratory acidosis. Key: (1) control; (2) 4 days, 2 to 3.5 per cent CO_2, (2Na) as in 2, plus medication of Na salt, 10 gm. daily; (2K) as in 2, plus medication of K salt, 10 gm. daily.

(*b*). Effect of alkalinizing agents (Na salt and K salt) on CO_2 dissociation curves in respiratory acidosis. Key: (1) control; (2) 4 days 2 to 3.5 per cent CO_2, (3) 2 hours, 5.5 to 6.0 per cent CO_2, following exposure to 2 to 3.5 per cent CO_2 for 4 days (1 to 3, 4 subjects); (3 Na) as in 3, plus medication of Na salt, 10 gm. daily; (3K) as in 3, plus medication of K salt, 10 gm. daily (3 Na and 3 K, 2 subjects). (Adapted from Pointner.[11])

mm. Hg CO_2 tension in tonometers at 37° C. The results are shown in FIGURES 7*a* and *b*. The well-known increase in the buffer capacity of blood in chronic respiratory acidosis is demonstrated in the elevation of the CO_2 dissociation curves (No. 2, FIGURES 7*a* and *b*). Medication of Na salt or K salt did not produce a further rise in the CO_2 dissociation curves after 5 days of exposure to 2 to 3.5 per cent CO_2 (FIGURE 7*a*). However, the subjects who had received buffer salts appeared to be more resistant to a 2-hour exposure of 5.5 to 6.0 per cent CO_2, following prolonged exposure to 2 to 3.5 per cent CO_2 for 5 days. Under these conditions, a fall of the CO_2 dissociation curves occurs (No. 3, FIGURE 7*b*) that is completely prevented by K salt treatment and reduced by Na salt medication (No. 3 K and 3 Na, FIGURE 7*b*).

Furthermore beneficial effects, particularly of potassium buffer salts, were

noted in the alleviation of symptoms (such as headaches, restlessness, and flights of thought) that developed during the initial phase commensurate with the uncompensated respiratory acidosis. However, symptoms associated with the second phase (compensated respiratory acidosis[12]), such as a general depression and apathy, did not seem to be relieved by potassium salt medication.

These findings, under conditions of a moderate chronic respiratory acidosis induced by a 4-day exposure to 2 to 3.5 per cent CO_2, indicate that oral medication of alkali salts does not raise the bicarbonate CO_2 level in the blood above a value reached by acid-base regulating mechanisms alone. Additional alkali, however, must be stored in tissues and made available during an acute exposure to a higher CO_2 concentration of 5.5 to 6 per cent CO_2 following chronic exposure to 2 to 3.5 per cent CO_2. This interpretation is in line with the findings of Swan *et al.*,[13] who demonstrated in nephrectomized dogs that 74 per cent of the infused bicarbonate was buffered from the tissues. The beneficial effects of these drugs in alleviating symptoms associated with the acute phase of respiratory acidosis are probably related to a more rapid restoration of the blood pH to normal. Compensation of the pH is accomplished without drugs within 3 days during exposure to 3 per cent CO_2.[5] Symptoms persisting during the chronic compensated phase of respiratory acidosis due to increased pCO_2 are apparently not influenced by oral alkali medications.

Discussion and Conclusions

In the described experiment with 1.5 per cent CO_2 a combination of respiratory and metabolic processes occur. A plot of the obtained pH and bicarbonate data shows that the values lie above the normal buffer line, indicating a combination of respiratory acidosis with a metabolic alkalosis, the latter due to renal compensation.

The question also might be raised whether a potassium deficiency develops during the compensated phase of respiratory acidosis secondary to an increased HCO_3^- excretion. If this had been the case, a decrease in the plasma K level should have developed during the 18-day period of exposure in which the HCO_3 excretion was markedly increased. However, the venous plasma potassium level showed no significant decrease.

Data on blood pH and pCO_2 homeostasis in chronic respiratory acidosis induced by prolonged exposure to 1.5 per cent CO_2 were shown to be related to specific changes in physiological functions. The significance of these established relationships depends to a certain extent on whether changes in blood pH produce corresponding changes in intracellular pH of tissues under these conditions, as is generally assumed, since no direct measurements on intracellular pH were obtained. There is evidence from studies on isolated tissues such as muscle that the intracellular pH is influenced very little by pH changes in the blood produced in acute experiments but is affected to a greater extent by changes in carbon dioxide tension of blood.[14]

These findings obtained with the DMO method are in agreement with others based on the CO_2 method of measuring intracellular pH.[15,16] E. D. Robin (elsewhere in these pages), using the DMO method for the determination of whole body intracellular pH determination in acute experiments with dogs,

steroid excretion. An effect of increased pCO_2 tension hardly could be influenced by amine therapy unless THAM absorbs some metabolic products that do not affect the acidity of the blood but are produced by the increased CO_2 level.

The astonishingly long time periods required for acclimatization and deacclimatization to such low CO_2 concentrations as 1.5 per cent CO_2 expressed, for example, in the persisting change in respiratory pattern and altered calcium metabolism[17] suggest that some kind of pathophysiological state might develop under these conditions. The results of animal experiments that showed an increase in kidney calcification of guinea pigs exposed to 1.5 per cent CO_2 for periods of from 40 to 93 days seem to support this concept.[18] It seems doubtful, therefore, whether long continued adaptation to slightly increased pCO_2 levels can be accomplished without altering normal physiological processes. This consideration has led to the formulation of a triple tolerance concept for chronic CO_2 toxicity,[19] which is expressed in FIGURE 8 together with a time concentration curve for adaptation to CO_2. Time for adaptation is defined as the time to reach a compensation of the respiratory acidosis induced by carbon dioxide inhalation. Determinations of pH, CO_2, bicarbonate levels, and electrolytes in blood and urine were used for estimations of the two phases in respiratory acidosis. The three levels of acidosis used for tolerance limits are listed in FIGURE 8. The level at which no significant physiological, psychological, and adaptation changes probably occur is estimated to be 0.5 to 0.8 per cent carbon dioxide in the inspired air.

Acknowledgment

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